DOI:
10.1016/j.biopsych.2018.10.015

Document Version
Peer reviewed version

Neural profile of callous traits in children: a population-based neuroimaging study

SELF-ARCHIVING VERSION

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Short title: Neural profile of pediatric callousness

Word count manuscript: 4000 (max. 4000)
Word count abstract: 250 (max. 250)
Number of tables and figures: 4 and 1, respectively
Supplemental information: 2 text section, 21 tables, and 3 figures
Keywords: structural neuroimaging; diffusion tensor imaging; callous-unemotional; epidemiology; sex differences; child psychiatry

Citation: Bolhuis K, Viding E, Muetzel RL, El Marroun H, Kocevska D, White T, Tiemeier H & Cecil CAM (In Press). Neural profile of callous traits in children: A population-based neuroimaging study. *Biological Psychiatry.*

Abstract

Background: Callous traits during childhood, e.g. lack of remorse and shallow affect, are a key risk marker for antisocial behavior. Although callous traits have been found to associate with structural and functional brain alterations, evidence to date has been almost exclusively limited to small, high-risk samples of boys. Here, we characterized gray and white matter brain correlates of callous traits in over 2000 children from the general population.

Methods: Data on mother-reported callous traits and brain imaging were collected at age 10 years from the Generation R Study. Structural MRI was used to investigate brain morphology using volumetric indices and whole-brain analyses (n=2146); diffusion tensor imaging (DTI) was used to assess global and specific white matter microstructure (n=2059).

Results: Callous traits were associated with lower global brain (e.g. total brain) volumes as well as decreased cortical surface area in frontal and temporal regions. Global mean diffusivity was negatively associated with callous traits, suggesting higher white matter microstructural integrity in children with elevated callous traits. Multiple individual tracts contributed to this global association, including the uncinate and cingulum. While no sex differences were observed for global volumetric indices, white matter associations were present only in girls .

Conclusions: This is the first study to provide a systematic characterization of the structural neural profile of callous traits in the general pediatric population. These findings extend previous work based on selected samples by demonstrating that childhood callous traits in the general population are characterized by widespread macro- and microstructural differences across the brain.

Introduction

Callous traits, including shallow affect, remorselessness, and a callous lack of empathy, are a key risk marker for antisocial behavior.(1) In childhood, callous traits are part of a broader set of callous-unemotional/psychopathic traits used to identify a particularly problematic subgroup of children with conduct problems, as operationalized by the DSM-5 specifier of "low prosocial emotions",(2) distinguished by more severe and chronic antisocial behavior and at least partially distinct etiology to their presentation.(3) Effects extend well beyond childhood, as callous traits independently predict a wide range of negative outcomes across the life-course, including adult psychopathy, antisocial personality disorder, criminality, and substance abuse.(4) Consequently, youth callous traits are an important target for etiologic research, prevention and intervention.(5)

A growing number of studies have been conducted to characterize the neurodevelopment of callous and related traits. Several different measures, varying in their coverage of specific behaviors, have been used to study callous-unemotional traits,(5,6) and this needs to be considered when interpreting the existing literature and, in particular, findings that have not replicated across studies. The majority of these have employed task-based functional magnetic resonance imaging (fMRI) in clinical/extreme samples of males.(7,8) Based on a recent meta-analysis of fMRI studies, which included 108 cases and 115 controls from 9 studies, youth with elevated psychopathic traits demonstrated decreased activity in ventromedial prefrontal cortex and the limbic system, and increased activation in fronto-striatal regions.(8) These regions are known to be involved in reward processing and affect regulation,(9) and partly converge with findings from structural MRI (sMRI) studies. Indeed, a recent meta-analysis including 188 cases and 122 controls pooled from 5 studies reported gray matter volume reductions of the putamen in youth with elevated callous-unemotional traits.(10) However, findings from structural studies regarding other brain regions have been inconsistent, likely due to heterogeneity in samples, analytic methods and participant age.(7,11) Finally, very few studies have employed diffusion tensor imaging (DTI) to characterize the microstructural properties of white matter associated with youth callous traits. Several studies have been published on externalizing behavior more broadly,(11) and we have recently demonstrated that lower whole-brain white matter connectivity was associated with more delinquent behavior in children.(12) Publications on callous traits specifically are more sparse with small samples, and these have reported mixed findings, with both increased and decreased white matter integrity observed in various tracts.(11) Most of these studies have uniquely focused on the uncinate fasciculus, a fiber bundle that connects prefrontal and subcortical structures, although recent work supports the involvement of a wider set of tracts.(13)

Overall, the above evidence points to neurobiological alterations associated with callous traits (and related phenotypes). However, knowledge on the neurodevelopmental underpinnings of callous traits is limited in four key ways. First, findings have been primarily based on small, selected samples, so

that it remains unclear to what extent structural brain differences are associated with callous traits in the general pediatric population. This is a notable gap, given compelling evidence that callous traits exist along a continuum in the general population.(14) Second, no neuroimaging study has examined both sMRI and DTI data to assess both gray and white brain structural correlates of youth callous traits–an important step towards integrating mixed findings in the literature. Third, existing studies have focused primarily on males due to the higher prevalence of conduct problems. As such, little is known about neuroanatomical correlates of callous traits in girls, and whether these differ from boys. Fourth, while previous imaging studies have largely focused on specific brain regions, it is important to employ a whole-brain approach to study callous traits as it is well-known from the wider neuroimaging literature that the brain functions in networks.(15)

Here we examined the relationship between brain structure and callous traits in over 2000 children, the largest neuroimaging study on pediatric callous traits to date, using data from a population-based cohort. Our aims were to assess both (i) structural brain morphology and (ii) white matter microstructure in relation to child callous traits. Both aims were addressed following a hierarchical approach, i.e. first global metrics were analyzed, followed by more detailed regional analysis if an association with global measures was observed. Based on existing literature, we expected global gray matter reductions as well as regional reductions in sub-cortical structure volumes. Regarding DTI analyses, we had no specific hypotheses given the mixed findings in the literature. Potential sex differences were also explored. However, because most prior neuroimaging studies have been based on males, we had no specific hypothesis.

Methods and Materials

Study population

This cross-sectional study was embedded in the Generation R Study, a prospective population-based cohort from Rotterdam, the Netherlands.(16) Study protocols were approved by the local ethics committee, and written informed consent and assent was obtained from all parents and children. At mean age ten years (range 8-11), mothers completed a questionnaire about their child's callous traits and children were invited to participate in a neuroimaging assessment.(17) For the current study, participants were included if they had data on callous traits and a sMRI scan or DTI scan available (*N*=2146, and *N*=2059, respectively, see Figure S1).

Measures

Callous traits

Callous traits were assessed through maternal report when the child was on average ten years old, using a brief validated questionnaire adapted from the Youth Self-Report and the Inventory for Callous-Unemotional Traits.(18) The questionnaire comprises 7 items on mainly interpersonal callous

traits, which were scored on a 4-point scale (range 0–21, see Figure S2), including "Does not find other people's feelings important", and "Is cold and indifferent". Although this measure does not comprehensively capture the full spectrum of unemotional or psychopathic traits, it has been shown to adequately capture childhood callous traits on a dimensional scale,(18) correlates strongly with other measures of youth psychopathy and is predictive of adult antisocial traits.(19) Endorsement of the seven items is shown in Table S1. The Cronbach's α in the current sample was 0.73.

Other behavioral data

At age 10 years, co-occurring emotional and behavioral problems at were assessed through mother-report and child-report using the well-validated Child Behavior Checklist and Brief Problem Monitor, respectively,(20,21) and mothers and children also completed the Strengths and Difficulties Questionnaire Prosocial scale.(22) Concurrently, maternal psychopathology was assessed through four subscales of the self-reported Brief Symptom Inventory.(23) Child intelligence (IQ) was measured at six years with the Snijders-Oomen non-verbal intelligence test.(24) See Supplement 1for more detailed information.

Brain imaging

An overview of the imaging procedure, sequences, and quality assessment has been described previously,(17) and can be found in Supplement 2. Every child was invited to participate in a mock scanning session prior to the MRI scan to familiarize them with the procedure. If at any point, she/he was too anxious about the procedure, they did not progress to the MRI scan. All images were acquired on a 3T GE MR750W Discovery scanner using an 8-channel head-coil.

Covariates

All analyses were adjusted for the following covariates. Child sex and date of birth were retrieved from birth records. Child ethnicity was defined according to the classification of Statistics Netherlands, i.e. Dutch, Other Western, and Other Non-Western. Maternal educational level was categorized into primary (no or primary education), secondary (lower and intermediate vocational training), and higher (higher vocational training and university) educational attainment.

Statistical analyses

Prior to the main analyses, we validated our measure of callous traits by examining whether correlations with mother- and child-reported emotional and behavioral problems, prosocial behavior, and IQ were in line with the previous literature. We then proceeded to examine neural correlates of callous traits, specifically (i) structural brain morphology and (ii) white matter microstructure, using separate linear regressions. All sMRI and DTI analyses were adjusted for covariates as described above. A hierarchical step-wise approach was conducted to limit the number of comparisons.

With respect to sMRI measures, first total global and sub-cortical volumetric indices were assessed in association with callous traits. Analyses pertaining to sub-cortical volumes were corrected for intracranial volume. A false-discovery rate (FDR) correction was applied to these analyses to address multiple testing.(25,26) If an association with any global measure was observed, subsequent vertex-wise analyses were conducted to investigate local differences in cortical morphology associated with callous traits.

With respect to DTI, initial analyses were performed with global FA and MD in association with callous traits. Next, if an association between global FA or MD and callous traits was observed, (1) subsequent analyses were conducted on individual white matter tracts and (2) associations with AD and RD (which are composites of MD, see Supplement 2) were explored. For these analyses, multiple-testing was addressed using an FDR-adjustment.

In sensitivity analyses, our models were additionally adjusted for co-occurring emotional and behavioral problems, non-verbal IQ and maternal psychiatric problems, in line with recent recommendations based on developmental studies.(3,27) In addition, sex differences of observed associations were explored using interaction analyses. Similarly, we investigated whether CBCL conduct problems moderated the association of callous traits with global volumetric and white matter outcomes. We also explored non-linear relationships by adding quadratic terms.

Because of skewness (Figure S2), callous traits sum scores were square root transformed to approach a normal distribution. Standardized coefficients are presented throughout. All analyses were conducted in R statistical software.(28) Missing values on covariates were dealt with using multiple imputations in MICE 2.25;(29) estimates from analyses of 100 imputed datasets were pooled.

Results

Behavioral validation of callous traits

As expected, callous traits showed high positive correlations with mother-reported conduct problems, followed by ODD and ADHD symptoms. In contrast, we observed significantly lower correlations for affective, anxiety and somatic symptoms (Table 1, difference in correlations, all Z-score>4.9, P<0.001). Similarly, child-reported externalizing and attention problems correlated more strongly with callous traits than internalizing problems (all Z-score>5.3, P<0.001). Mother-reporte and child-reported prosocial behavior were negatively correlated with callous traits.

Structural brain morphology

Total brain, cortical gray matter, and white matter volumes were all negatively associated with callous traits (Table 2). Right amygdala volume was negatively associated with callous traits, which did not

survive FDR-correction. No associations were found between sub-cortical volumes and callous traits. Similar results were observed in analyses with additional adjustment for co-occurring psychiatric problems, non-verbal IQ, and maternal psychopathology (Table S2- S4). In vertex-wise analyses, ten brain regions showed negative correlations between cortical surface area and callous traits (Table 3, Figure 1), which were localized in the frontal and temporal lobes of both hemispheres. No vertex-wise associations were found between cortical thickness and callous traits. Three gyrification clusters in the temporal lobe were negatively associated with callous traits (Table S5). Additional adjustment for IQ and maternal psychopathology did not considerably alter these observations (Table S7-S8), but after adjustment for co-occurring psychiatric problems only the superior frontal gyrus was associated with callous traits (Table S6).

White matter microstructure

Global MD, but not global FA, was negatively associated with callous traits (Table 2). Similarly, global AD and RD were negatively associated with callous traits (Table S9). Several white matter tracts contributed to this global association (Table 4), including the superior longitudinal fasciculus, corticospinal tract, uncinate and cingulum. These associations all survived FDR-correction. Comparable results were observed in analyses with additional adjustment for co-occurring psychiatric problems, non-verbal IQ, and maternal psychopathology (Table S2-4; S10-S12). Callous traits were negatively associated with AD of the inferior and superior longitudinal fasciculi and corticospinal tract, and with uncinate and cingulum RD (Table S13). A visualization of the associated white matter tracts is presented in Figure S2.

Sex interaction analyses

Callous traits were significantly higher in boys than in girls (2.33 versus 1.85, t=5.1, P<0.001). Boys scored higher on almost all callousness items (Table S14-15); correlations between behavioral problems and callous traits were similar across sexes. Non-verbal IQ negatively correlated with callous traits in boys but not in girls (Table S16). No interaction was observed for structural volumetric measures (Table S17). A significant gender-by-brain interaction was observed for the associations of MD with callous traits (P=0.005). Stratified analyses demonstrated that our findings in the full sample were driven by the associations in girls, and these effects were observed in several tracts across the brain (Table S18-S19). No such associations were found in boys.

Sensitivity analyses

Conduct problems did not moderate the associations of callous traits with global volumetric and white matter outcomes (Table S20). Associations with quadratic terms were all non-significant (Table S21).

Discussion

This is the first study to characterize the structural neural profile of callous traits in the general pediatric population. Based on sMRI and DTI data from over 2000 children, we demonstrate that callous traits at age 10 are characterized by widespread macrostructural and microstructural differences across the brain. We highlight three key findings. First, childhood callous traits were associated with reduced global gray matter, and decreases in cortical surface area and gyrification across several frontal and temporal areas. These observations are consistent with prior research using high-risk samples. Second, we observed increased global white matter microstructure in children with elevated callous traits, suggesting increased white matter integrity across various white matter tracts. Third, we found that white matter–but not gray matter–associations differed by sex, with associations only observed in girls. Together, the present findings contribute to a more complete understanding of the relationship between brain structure and callous traits, and may be used as a guiding framework for future research to uncover causal neurodevelopmental pathways.

Findings from the sMRI analyses indicated that callous traits are associated with lower global brain volumes. More specifically, decreased cortical surface area and reduced gyrification was observed in various brain regions, including the temporal gyri and several (pre-)frontal gyri. These regions have previously been associated with behavioral inhibition, social cognition, and emotion regulation,(30-33) which have been implicated in the development of callousness.(3,6) Our findings corroborate studies that observed gray matter volume reductions in orbitofrontal, cingulate, and temporal cortices in older youths with callous traits in the clinical range,(10) and support others that observed reduced cortical surface or gyrification across similar regions.(34-37) We identified a nominally significant association between callous traits and lower right amygdala volume, which did not survive multiple-testing correction when accounting for other subcortical regions. While aberrant amygdala function has been robustly associated with callous-unemotional traits,(8) structural volumetric differences of the amygdala are rarely observed.(10,38-41) This inconsistency between structural and functional neuroimaging findings could partly be explained by the use of different significance thresholds in studies taking a region-of-interest vs. whole-brain approach. Our findings suggest the involvement of many regions with small effects. By extending these clinical MRI studies, our findings corroborate the notion that callous traits exist along a continuum in the general population, which has also been evidenced in genetic studies.(3,5,14) Moreover, associations remained consistent after additional adjustment for co-occurring emotional, behavioral and attention problems, IQ, and maternal psychopathology. In other words, while callous traits were significantly associated with other psychiatric symptoms (including conduct and ADHD problems) and IQ–consistent with the extant literature–these comorbid symptoms did not explain our global neuroimaging findings. Co-occurring emotional and behavioral problems did, however, account for a large portion of the explained variance in vertex-wise cortical surface area analyses, supporting the presence of at least some shared neural

alterations in callous traits and comorbid psychiatric problems.(3,4) Of interest, unique variance for callous traits was observed in the superior frontal gyrus, which has been linked to callous traits in clinical cohorts.(36,38)

Whereas structural brain connectivity has been examined in the context of externalizing problems more generally,(11,12) few studies to date have examined the white matter microstructure profile of callous traits. This work has mainly focused on the uncinate fasciculus in older, selected samples, and produced mixed results, reporting both lower and higher microstructure in adolescents with elevated callous traits.(11,42) Two studies employing a whole-brain approach–both of which are based on data from adolescent (primarily males) arrestee cohorts–reported that callous traits were associated with higher white matter integrity in many tracts across the brain, including the corticospinal tract, superior longitudinal fasciculus and uncinate.(13,43) These findings are consistent with the higher microstructural integrity in various tracts observed in the current study, e.g. uncinate and cingulum, which connect frontal with temporal/parietal brain regions.(44-46) This is noteworthy considering the substantial differences in design and sample characteristics between these studies and ours, including the focus on different developmental periods, proportion of boys/girls, and the use of a high-risk versus general population sample. The decreases in MD identified across these studies suggest *higher* white matter microstructure, possibly indicating accelerated or precocious white matter development in children with elevated callous traits.(15) Importantly, decreased integrity has also been observed within high-risk samples.(44-46) The reason for such discrepancy is unclear, potential reasons include different sampling strategies, varying levels of exposure to adversities and comorbid psychiatric problems, case-control versus dimensional perspectives, and different definitions of the callousness phenotypes. Our current findings are in contrast with our previous publication where we showed *lower* white matter microstructure in pre-adolescent children with elevated levels of delinquent behavior,(12) suggesting that callous traits and other externalizing behaviors are associated with differential neural correlates even though these behaviors are correlated. This is consistent with fMRI studies showing, for example, amygdala reactivity to fearful faces to be negatively associated with callous traits and positively associated with conduct problems across multiple independent samples, despite these psychiatric phenotypes being positively correlated with one another.(47-49) Findings from sMRI and DTI have been much less consistent,(10,11) although differential amygdala volume reductions have been observed for callous-unemotional versus conduct problems.(50,51) In this study, conduct problems were not found to moderate associations between callous traits and global brain measures. Importantly, in sensitivity analyses we adjusted for all co-occurring problems, which left our sMRI and DTI findings unchanged even though callous traits were substantially correlated with externalizing behaviors. This, together with our previous observations,(12) suggests specific brain-callousness correlates independent of other types of psychopathology, indicating that there is added value in screening for callous traits in children at elevated risk for antisocial behavior.

This is the first study to examine neural correlates of callous traits using both sMRI and DTI. Overall, our findings corroborate (1) previous high-risk sMRI studies reporting associations between callous traits and *lower* brain volume across frontal and temporal regions; and (2) previous high-risk DTI studies indicating *higher* microstructural integrity of the white matter tracts connecting these areas.(13,35,36,38,42,43). As such, our findings support these seemingly discrepant associations, and suggest that these are not simply the result of methodological differences between studies. The inverse relationship between the sMRI and DTI findings could potentially indicate decreased cortical functioning and consequently more dysregulated white matter connectivity, or vice versa.(15) Multi-modal neuroimaging approaches incorporating fMRI assessments are required to disentangle the origins of these observations.

While boys and girls are known to differ considerably in prevalence of callous traits and trajectories of brain development,(3,52) it is unclear whether there are sex differences in the neural profile of callous traits, as existing studies have primarily focused on males. The equal distribution of boys and girls in our sample offered a unique opportunity to address this gap. We found no sex differences in global volumetric measures. However, we did find that the relation of global white matter microstructure with callous traits was only significant in girls. Given that white matter has been shown to develop more quickly in girls compared with boys,(52) it is possible that our findings reflect advanced white matter maturation in girls with elevated callous traits and thus potential residual (brain) age confounding. In *post-hoc* analyses, we found that age did not moderate the association of global MD, AD or RD with callous traits in girls (all $P>0.100$). However, potentially chronological age does not adequately capture differences in neurobiological maturation.(53) Recent smaller studies have observed more pronounced cortical differences for callous traits in adolescent boys versus girls,(54) which is not what we observed here. These findings could potentially signify that callous traits and their associated neural profile reflect differential development in girls compared with boys. Repeated neuroimaging assessments at later ages–in combination with pubertal development measures–will be particularly valuable for clarifying whether these sex differences persist across brain development or whether the developmental trajectories are similar for boys and girls, with possibly different onsets.

Our study had several strengths, including the use of a large sample of non-selected children from the community and the analysis of both sMRI and DTI data. Our hierarchical analytical approach allowed us to investigate both global and specific brain metrics without substantially increasing the risk of type II error. Stringent sensitivity analyses further enabled us to ascertain that our findings were robust to additional adjustment for co-occurring psychiatric problems, IQ, and maternal psychopathology. Finally, our study was the first to examine neuroanatomical correlates of callous traits in a sample with an equal distribution of boys and girls. Despite these strengths, several limitations should be noted. First, our measure of callous traits did not adequately cover unemotional/affective aspects, which are

important features of callous-unemotional and broader psychopathic traits, and which have been studied in the wider literature in clinical samples.(5) Future work will need to take this limitation into account by exploring associations across a broader spectrum of traits(6) and, additionally, employ a multi-informant approach to childhood callous traits. Second, our findings were cross-sectional and, hence, should be interpreted as a neurobiological characterization of callous traits, rather than an underlying biological mechanism. Furthermore, we were unable to assess whether observed brain-behavior associations predicted functional outcomes, both concurrently and longitudinally, such as academic performance. Furthermore, the participants are still too young (i.e. do not have enough variability in behavior) for examining other relevant functional domains, such as substance use, risk-taking, and contact with law enforcement. In future, it will be important to draw on longitudinal designs with repeated measures of neuroimaging and callous traits in order to trace neurodevelopmental trajectories of callous traits and their utility for predicting clinically relevant outcomes in later life. Third, a growing body of literature points to the existence of distinct developmental pathways to youth callous traits,(3) with groups being differentially related to exposure to early adversity in childhood and accompanied anxiety symptoms, and the other group who develops similarly severe callous traits through inherited vulnerabilities.(3) Our current population-based cross-sectional design did not allow us to study these differential developmental pathways. Repeated assessments of both neuroimaging and callous traits across childhood are needed, particularly with regards to differential developmental pathways.(55,56) Nevertheless, we adjusted for behavioral as well as emotional problems in sensitivity analyses, which did not alter our main findings. Fourth, non-verbal IQ was assessed 4 years prior to callous traits and MRI assessments; it would have been better to have concurrent assessments of each. Despite this, intelligence is moderately stable during childhood,(57) which supports the reliability of our analysis with adjustment for IQ at 6 years. Fifth, while our hierarchical analysis approach reduces the likelihood of false positives, it also increases chances of false negatives, i.e. very focal findings might have been obscured if global associations were not found. Sixth, while the Generation R Study is an ethnically diverse study, most participants are of European descent. More research needs to be conducted in non-white populations, which is a considerable gap in the literature. Finally, more research should employ multi-modal approaches, for example integrating fMRI data to further characterize the neural profile of callous traits .

In conclusion, we found evidence for widespread macro- and microstructural brain alterations in callous traits based on a large community sample of children . These results underscore that youth callous traits are not uniquely associated with brain differences in frontal-limbic or frontal-striatal connections; rather, structural brain differences were observed in a wide range of areas across the brain. Our study provides further support for the value of conceptualizing pediatric callous traits as a neurodevelopmental condition. Priority should be given to prospective developmentally-sensitive research, which will enable to examine early environmental and neurobiological pathways to callous

traits, potential sex differences, and their utility in predicting clinically relevant functional domains in later life. Finally, the current results might indicate that children with elevated callous traits show differences in brain development, which holds promise for etiologic research for a better understanding of the development of severe antisocial behavior later in life.

Acknowledgements

This work was supported by the European Union Seventh Framework Program (FP7/2007-2013): ACTION: Aggression in Children: Unravelling gene-environment interplay to inform Treatment and InterventiON strategies (grant number 602768), the Netherlands Organization for Scientific Research (NWO-grant 016.VICI.170.200) to HT, and the Netherlands Organization for Health Research and Development (ZonMw) TOP project number 91211021 to TW. CC is supported by the Economic and Social Research Council (grant ref: ES/N001273/1). EV is a Royal Society Wolfson Research Merit Award holder. Super computing resources were made possible through the NOW Physical Sciences Division (surfsara.nl). The first phase of the Generation R Study is made possible by financial support from the Erasmus Medical Centre, Rotterdam; the Erasmus University Rotterdam; The Netherlands Organization for Health Research and Development (ZonMw). The authors gratefully acknowledge the contribution of all children and parents, general practitioners, hospitals, midwives, and pharmacies involved in the Generation R Study. The Generation R Study is conducted by the Erasmus Medical Center (Rotterdam) in close collaboration with the School of Law and Faculty of Social Sciences of the Erasmus University Rotterdam; the Municipal Health Service Rotterdam area, Rotterdam; the Rotterdam Homecare Foundation, Rotterdam; and the Stichting Trombosedienst & Artsenlaboratorium Rijnmond, Rotterdam.

Financial disclosures

The authors have declared that there are no conflicts of interest in relation to the subject of this study.

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FIGURE LEGENDS

Figure 1: Negative associations between cortical surface area and callous traits (N = 2146)

Note: Analyses are corrected for age, sex, child ethnicity and maternal educational level. Colors represent the cluster forming thresholds. Blue clusters represent a negative correlation between cortical surface area and callous traits at a cluster-wise corrected *P*-value threshold of <0.05, with transition to light-blue, purple and white for clusters that are negatively correlated with callous traits at more stringent *P*-value thresholds (i.e. 0.01, 0.005, 0.001, respectively; see legend in Figure). LH: left hemisphere; RH: right hemisphere. Numbers of the clusters correspond to the numbers shown in Table 3.

TABLES

Table 1: Sample characteristics

	N (% missing data)	Descriptive statistics	Correlation with callous traits, *r*
Child characteristics			
Age at MRI, mean (SD)	2146 (0% missing)	10.10 (0.58)	-
Sex, proportion girls	2146 (0% missing)	49.9%	-
Ethnicity	2132 (0.7% missing)		
Dutch		68.6	-
Other, Western		8.3	-
Other, non-Western		22.8	-
Callous traits, median (IQR)	2146 (0% missing)	2.00 (3.00)	-
Non-verbal IQ at age 6 years, mean (SD)	1904 (11.3% missing)	104.4 (14.64)	-0.08**
Mother-reported CBCL, median (IQR)			
Affective Problems	2078 (3.3% missing)	1.00 (2.00)	0.23**
Anxiety Problems	2074 (3.5% missing)	0.00 (2.00)	0.15**
Somatic Complaints	2062 (3.9% missing)	0.00 (2.00)	0.09**
ADHD Problems	2073 (3.4% missing)	2.00 (4.00)	0.36**
ODD Problems	2071 (3.6% missing)	1.00 (2.00)	0.39**
CD Problems	2078 (3.3% missing)	0.00 (1.00)	0.47**
Child-reported BPM, median (IQR)			
Internalizing problems	2044 (4.8% missing)	2.00 (3.00)	0.07**
Externalizing problems	2042 (4.8% missing)	2.00 (3.00)	0.22**
Attention problems	2042 (4.8% missing)	3.00 (3.00)	0.20**
SDQ – Prosocial scale, median (IQR)			
Mother-reported	2098 (2.2% missing)	9.00 (2.00)	-0.22**
Child-reported	2056 (4.2% missing)	9.00 (2.00)	-0.12**
Maternal characteristics			
Educational level, %	2020 (6.0% missing)		
High		66.7	
Medium		31.7	
Low		1.6	

Note: ** $P < 0.01$

Abbreviations: SD, standard deviation; IQR, interquartile range; IQ, intelligence quotient; CBCL, Child Behavior Checklist; ADHD, attention deficit/hyperactivity disorder; ODD, oppositional defiant disorder; CD, conduct disorder; BPM, Brief Problem Monitor; SDQ, Strengths and Difficulties Questionnaire

Table 2: Association of global structural volumetric and global white matter microstructural measures with callous traits.

	Callous traits		
	β (95% CI)	*P*	FDR-adjusted *P*
Structural volumetric measures (*N* = 2146)			
Total brain volume	-0.10 (-0.15;-0.05)	<0.001	-
Cortical grey matter volume	-0.10 (-0.15;-0.05)	<0.001	<0.001
White matter volume	-0.08 (-0.13;-0.03)	0.001	0.003
Subcortical structures			
Left amygdala	-0.03 (-0.08;0.02)	0.194	0.652
Right amygdala	-0.06 (-0.11;-0.01)	0.030	0.420
Left hippocampus	-0.03 (-0.08;0.02)	0.233	0.652
Right hippocampus	-0.02 (-0.07;0.04)	0.559	0.862
Left thalamus	0.00 (-0.06;0.06)	0.950	0.987
Right thalamus	-0.03 (-0.09;0.03)	0.361	0.760
Left caudate	-0.03 (-0.08;0.02)	0.223	0.652
Right caudate	-0.04 (-0.09;0.01)	0.132	0.652
Left putamen	-0.01 (-0.06;0.04)	0.616	0.862
Right putamen	0.00 (-0.05;0.05)	0.987	0.987
Left globus pallidus	0.00 (-0.05;0.05)	0.956	0.987
Right globus pallidus	-0.01 (-0.06;0.03)	0.562	0.862
Left nucleus accumbens	0.02 (-0.03;0.07)	0.380	0.760
Right nucleus accumbens	0.01 (-0.04;0.05)	0.751	0.956
White matter microstructural measures (*N* = 2059)			
Global fractional anisotropy (FA)	0.01 (-0.03;0.06)	0.633	-
Global mean diffusivity (MD)	-0.06 (-0.11;-0.02)	0.006	-

Note: All analyses are corrected for child sex, child age at MRI visit, child ethnicity, and maternal educational level. Sub-cortical volumes are additionally adjusted for intracranial volume. Estimates reflect standardized coefficients.

Table 3: Vertex-wise analyses of cortical surface area and callous traits (N = 2146).

Hemisphere and region	Cluster size (mm^2)	Talairach Coordinates (x, y, z)	Number of Vertices within Cluster	β (average across cluster)	Cluster-wise *P*-values
Left					
1. Fusiform	1476.88	-41.8, -47.3, -14.0	2445	-0.08	0.0001
2. Superior temporal	918.28	-51.8, 8.0, -18.0	1718	-0.07	0.0001
3. Lingual	681.36	-20.7, -54.0, -2.9	1422	-0.08	0.0003
4. Superior frontal	522.48	-13.7, 45.9, 3.5	973	-0.08	0.0016
5. Post-central	457.15	-51.7, -12.5, 15.9	1209	-0.06	0.0036
6. Lateral orbitofrontal	357.56	-32.2, 26.6, -10.3	727	-0.07	0.0127
Right					
7. Middle temporal	1446.11	49.3, 7.5, -32.9	2541	-0.08	0.0001
8. Fusiform	545.16	41.6, -46.3, -16.6	1066	-0.06	0.0012
9. Isthmus of the cingulate	411.04	6.0, -20.1, 20.9	1036	-0.07	0.0065
10. Post-central	396.81	60.0, -8.2, 15.9	872	-0.07	0.0077

Note: Analyses are corrected for age, sex, child ethnicity and maternal educational level. Numbers of the clusters correspond to the numbers shown in Figure 1. Cluster forming threshold of 0.001.

Table 4: Associations between mean diffusivity (MD) in individual white matter tracts and callous traits.

	β (95% CI)	*P*	FDR-adjusted *P*
Inferior longitudinal fasciculus	-0.04 (-0.09;0.00)	0.072	0.089
Superior longitudinal fasciculus	-0.06 (-0.11;-0.01)	0.010	0.021
Forceps minor	-0.04 (-0.08;0.00)	0.076	0.089
Forceps major	-0.01 (-0.06;0.03)	0.528	0.528
Corticospinal tract	-0.15 (-0.26;-0.04)	0.008	0.021
Uncinate fasciculus	-0.06 (-0.11;-0.02)	0.002	0.014
Cingulum bundle	-0.06 (-0.10;-0.01)	0.012	0.021

Note: All analyses are corrected for child sex, child age at MRI visit, child ethnicity, and maternal educational level. Microstructural properties of left and right tracts were combined and weighted for their respective volumes, except for forceps minor and major. Estimates reflect standardized coefficients.

Neural Profile of Callous Traits in Children: A Population-Based Neuroimaging Study

SUPPLEMENTARY INFORMATION

Supplemental Methods

Description other behavioral data

Co-occurring emotional and behavioral problems (age 10)

At the same time point, i.e. child age 10 years, mothers completed the school-age version of Child Behavior Checklist (CBCL/6-18) to rate emotional and behavioral problems of the child.(1) The CBCL covers a broad range of emotional and behavioral problems which were rated on a 3-point scale (0 = not true, 1 = sometimes/somewhat true, 2 = very/often true). The CBCL is a widely used and validated measure for child and adolescent behaviour problems on a continuous scale, and has been shown to predict clinical psychiatric diagnoses in adulthood.(2,3) Individual items can be summed to obtain a total problems score, and items load on 6 independent DSM-based scales of internalizing and externalizing problems, i.e. affective problems, anxiety problems, somatic problems, attention-deficit/hyperactivity problems, oppositional defiant problems, and conduct problems. Similarly, child self-reported problems were assessed at age 10 years, for which the Brief Problem Monitor (BPM) was used.(4) The BPM encompasses three scales of internalizing, externalizing and attention problems and is a validated abbreviated child-reported version of the CBCL. In the current study, mother-reported and child-reported problems were correlated with the callous traits sum score to obtain external behavioral validation of our measure of callous traits. In addition, CBCL total scores were used in a sensitivity step in our main analyses in order to examine the extent to which our observed associations were explained by co-occurring emotional and behavioral problems.

Prosocial behavior (age 10)

At mean age ten years both mothers and children completed the prosocial scale of the Strengths and Difficulties Questionnaire (SDQ; (5)). This scale comprises five items, such as "[My child / I often spontaneously offers to help others", which are rated on a three-point scale (1 = not true, 2 = somewhat/sometimes true, 3 = certainly/always true). The prosocial scale of the SDQ has been shown to have acceptable test-retest reliability and construct validity. Together with the mother- and child-reported problems described above, prosocial behavior was used in the current study as an external behavioral validation of our measure of callous traits.

Non-verbal intelligence (age 6)

Child intelligence (IQ) was measured at age 6 using the Snijders-Oomen nonverbal intelligence test.(6) At this developmental stage, a nonverbal IQ assessment is the preferred method and this measure has been shown to reliably determine non-verbal cognitive ability in early childhood.(7)

Maternal psychiatric problems (age 10)

Psychiatric problems of the mother were assessed with the Brief Symptom Inventory (BSI), when the children were at mean age 10 years.(8) Four validated subscales were used, i.e. interpersonal

sensitivity, depression, anxiety and hostility, of which a sum score was calculated. The BSI is a validated, reliable measure to continuously examine adult psychiatric problems along a continuum.

Supplemental Methods

Brain imaging method

Image acquisition

After a localizer, a structural T1 scan was the first sequence to be performed, followed by the DTI. Structural images were processed through the FreeSurfer analysis suite, version 6.0.(9) DTI pre-processing was conducted using the FMRIB Software Library (FSL), version 5.0.9.(10) For structural MRI analyses, global metrics of volume were extracted. In addition, separate whole-brain vertex-wise analyses were performed to examine cortical thickness, cortical surface area, and gyrification in association with callous traits. With respect to DTI, probabilistic white matter fiber tractography was conducted on each child's DTI images and fractional anisotropy (FA) mean diffusivity (MD), axial diffusivity (AD) and radial diffusivity (RD) were computed for each tract. Global brain FA, MD, AD and RD were computed based on 12 well-studied white matter tracts, as described previously.(11) Head movement was addressed by accommodating the child as much as possible, through detailed explanation and reassurance before the MRI scanning session, the option to watch a movie during scanning, and cushions were put next to the child's head to limit further head motion. After a localizer, T1-weighted structural images were acquired with an inversion recovery-prepared fast spoiled gradient recalled sequence. The following sequence parameters were used with the GE option *BRAVO*: TR = 8.77ms, TE = 3.4ms, TI = 600ms, Flip Angle = 10°, FOV = 220mm x 220mm, Acquisition Matrix = 220 x 220, slice thickness = 1mm, number of slices = 230, voxel size = 1mm x 1mm x 1mm, ARC Acceleration = 2. The DTI scan was acquired using an axial spin echo, echo planar imaging sequence with 3 b = 0 scans and 35 diffusion weighted images (TR = 12,500ms, TE = 72.8ms, Field of view = 240mm x 240mm, Acquisition Matrix = 120 x 120, slice thickness = 2mm, voxel size = 2mm x 2mm x 2mm, number of slices = 65, Asset Acceleration = 2). Children with an incidental structural brain abnormality were excluded from both the sMRI and DTI analyses (see Figure S1).

Structural image processing and quality assurance

Structural images were processed through the FreeSurfer analysis suite, version 6.0(9). Freesurfer morphometry has demonstrated good test-retest reliability across scanner manufacturers and field strengths.(12,13) In summary, non-brain tissue was removed, voxel intensities were normalized for B_1 inhomogeneity, whole-brain tissue segmentation was performed, and a surface-based model of the cortex was reconstructed. Global metrics of volume (i.e. total brain volume, total cortical grey matter volume, white matter volume, amygdala and hippocampus volumes) were extracted. Freesurfer

reconstructions were visually inspected using a previously described protocol,(14,15) and image datasets not suitable for analysis were excluded from the final sample. In brief, the white and pial surface representations for all subjects were inspected for accuracy against the brain image at a number of slices in different plains, i.e. axial, coronal and sagittal. Additional inspection with a metric of automated structural neuroimaging quality assessment(16) revealed that this index was not associated with callous traits (r = -0.01, 95%CI -0.06-0.02, P = 0.409).

Vertex-wise analyses

Whole-brain cortical morphological analyses were performed to obtain more detailed information of morphological correlates of callous traits. These vertex-wise analyses were conducted using in house R package (https://github.com/muet0005/QdecR) that allows for inter-subject/group averaging and inference using the general linear model on the morphometric data produced by the FreeSurfer preprocessing stream. Thickness, surface area, and local gyrification maps from each subject were co-registered to a common stereotaxic space, and subsequently smoothed with either a 10mm (thickness and surface area) or 5mm (local gyrification) Gaussian kernel. Analyses were corrected for multiple comparisons using the built-in Monte Carlo simulation at thresholds varying from $P < 0.05$ to 0.001, a cluster-wise correction that controls for the rate of false positive clusters. Further, cluster-wise p-values were adjusted for running analyses in both left and right hemispheres. Results were shown for all clusters to demonstrate the magnitude of association with callous trait for each cluster.

DTI pre-processing

Diffusion tensor imaging scanning pre-processing was conducted using the FMRIB Software Library (FSL), version 5.0.9.(10) Image processing has been described in more detail elsewhere.(17) In short, non-brain tissue was removed and diffusion images were corrected for eddy current-induced artefacts and translations/rotations resulting from head motion. The diffusion tensor was fitted at each voxel using the RESTORE method from the Camino diffusion MRI toolkit,(18) and scalar metrics (i.e. fractional anisotropy [FA], mean diffusivity [MD], axial diffusivity [AD] and radial diffusivity [RD]) were subsequently computed. FA described the directional degree of diffusion of water and ranges from 0 to 1, with 0 being completely isotropic (i.e. diffusion equal in all directions) and 1 being completely anisotropic (i.e. diffusion along only one axis). MD simply describes the average diffusion in all directions and is composed of AD (i.e. axial diffusivity) and RD (i.e. radial diffusivity).

White matter probabilistic tractography

Probabilistic white matter fiber tractography was conducted on each child's DTI images using the automated FSL plugin *AutoPtx*,(19) to identify connectivity distributions for a number of large fibre bundles such as the uncinate fasciculus and cingulum bundle. Subsequently, connectivity distributions were normalised based on the number of successful seed-to-target attempts, and then thresholded to

remove voxels that were unlikely to be part of the true distribution. Average FA and MD values were computed for each white matter tract by weighting voxels based on the connectivity distribution (i.e., FA in voxels with higher probabilities received higher weight). Left and right white matter tract metric values were averaged and weighted for their respective volumes as we had no a priori hypotheses regarding the laterality of white matter tracts associated with callous-unemotional traits.

DTI quality assurance

First, the DTIPrep tool (https://www.nitrc.org/projects/dtiprep/) was used to automatically examine data for slice-wise variation and characteristics of artefact in each diffusion-weighted volume. Second, the sum-of-squares error (SSE) maps from the diffusion tensor calculations were examined for structured signal that was indicative of artefact. Each SSE map was rated from 0 to 3 (0: "None", 1: "Mild", 2: "Moderate", 3: "Severe"). Cases not excluded by the automated DTIPrep tool but had a "Severe" score from the SSE rating were excluded from analyses. Further, processed tractography data were examined on their quality. Next, the registration of the DTI data to standard space was inspected for accuracy. Additional quality assessment inspection with the number of slices or volumes affected by motion, cardiac pulsation or other artefacts(11) demonstrated that these QA indices were not correlated with callous traits (number of total affected slices: r = -0.01, 95% CI -0.05-0.03, P = 0.687; number of total affected volumes: r = 0.00, 95%CI -0.04-0.05, P = 0.869).

Supplementary Table S1: Endorsement of the mother-reported callous traits items in the current sample (*N* = 2159).

	Does not apply at all, *n* (%)	Does apply slightly, *n* (%)	Does apply very much, *n* (%)	Does apply completely, *n* (%)
Cannot be trusted with regard to what he/she says	1721 (80.5)	382 (17.9)	21 (1.0)	13 (0.6)
Denies having done something wrong, even though it is certain he/she did do something wrong	1146 (53.5)	922 (43.1)	58 (2.7)	15 (0.7)
Uses or misleads other people in order to get what he/she wants	1784 (83.3)	330 (15.4)	20 (0.9)	8 (0.4)
If confronted about his/her behaviour, he/she is able to talk him/herself out of it easily	1174 (55.1)	745 (35.0)	166 (7.8)	45 (2.1)
Does not keep any promises	1428 (66.9)	647 (30.3)	46 (2.2)	13 (0.6)
Does not find other people's feelings important	1801 (84.2)	286 (13.4)	40 (1.9)	13 (0.6)
Is cold and indifferent	2017 (94.4)	105 (4.9)	9 (0.4)	5 (0.2)

Supplementary Table S2: Association of global structural volumetric and global white matter microstructural measures with callous traits, with additional adjustment for co-occurring emotional and behavioral problems.

	Callous traits	
	β (95% CI)	*P*
Structural volumetric measures (*N* = 2146)		
Total brain volume	-0.07 (-0.12;-0.03)	0.002
Cortical grey matter volume	-0.07 (-0.12;-0.03)	0.002
White matter volume	-0.06 (-0.10;-0.01)	0.009
Subcortical structures		
Left amygdala	-0.03 (-0.08;0.01)	0.159
Right amygdala	-0.05 (-0.10;-0.01)	0.026
Left hippocampus	-0.02 (-0.07;0.02)	0.329
Right hippocampus	-0.01 (-0.05;0.04)	0.741
Left thalamus	0.01 (-0.05;0.06)	0.849
Right thalamus	-0.02 (-0.08;0.04)	0.471
Left caudate	-0.02 (-0.06;0.03)	0.482
Right caudate	-0.02 (-0.07;0.03)	0.392
Left putamen	-0.02 (-0.07;0.02)	0.349
Right putamen	0.00 (-0.04;0.05)	0.935
Left globus pallidus	-0.01 (-0.05;0.04)	0.746
Right globus pallidus	-0.02 (-0.07;0.02)	0.348
Left nucleus accumbens	0.03 (-0.01;0.07)	0.173
Right nucleus accumbens	0.01 (-0.03;0.05)	0.615
White matter microstructural measures (*N* = 2059)		
Global fractional anisotropy (FA)	0.02 (-0.02;0.06)	0.236
Global mean diffusivity (MD)	-0.06 (-0.10;-0.02)	0.005

Note: All analyses are corrected for child sex, child age at MRI visit, child ethnicity, maternal educational level, and CBCL total problems scores. Sub-cortical volumes are additionally adjusted for intracranial volume. Estimates reflect standardized coefficients.

Supplementary Table S3: Association of global structural volumetric and global white matter microstructural measures with callous traits, with additional adjustment non-verbal IQ.

	Callous traits	
	β (95% CI)	*P*
Structural volumetric measures (*N* = 2146)		
Total brain volume	-0.10 (-0.15;-0.05)	<0.001
Cortical grey matter volume	-0.10 (-0.15;-0.05)	<0.001
White matter volume	-0.08 (-0.12;-0.03)	0.003
Subcortical structures		
Left amygdala	-0.03 (-0.08;0.02)	0.217
Right amygdala	-0.05 (-0.11;0.00)	0.038
Left hippocampus	-0.03 (-0.08;0.02)	0.247
Right hippocampus	-0.01 (-0.07;0.04)	0.585
Left thalamus	0.00 (-0.06;0.06)	0.982
Right thalamus	-0.03 (-0.09;0.03)	0.371
Left caudate	-0.03 (-0.08;0.02)	0.261
Right caudate	-0.04 (-0.09;0.01)	0.155
Left putamen	-0.01 (-0.06;0.04)	0.598
Right putamen	0.00 (-0.05;0.05)	0.988
Left globus pallidus	0.00 (-0.05;0.05)	0.976
Right globus pallidus	-0.01 (-0.06;0.04)	0.600
Left nucleus accumbens	0.02 (-0.03;0.07)	0.427
Right nucleus accumbens	0.01 (-0.04;0.05)	0.748
White matter microstructural measures (*N* = 2059)		
Global fractional anisotropy (FA)	0.02 (-0.03;0.06)	0.438
Global mean diffusivity (MD)	-0.07 (-0.11;-0.02)	0.006

Note: All analyses are corrected for child sex, child age at MRI visit, child ethnicity, maternal educational level, and non-verbal IQ of the child. Sub-cortical volumes are additionally adjusted for intracranial volume. Estimates reflect standardized coefficients.

Supplementary Table S4: Association of global structural volumetric and global white matter microstructural measures with callous traits, with additional adjustment maternal psychiatric problems.

	Callous traits	
	β (95% CI)	*P*
Structural volumetric measures (*N* = 2146)		
Total brain volume	-0.10 (-0.15;-0.05)	<0.001
Cortical grey matter volume	-0.10 (-0.15;-0.05)	<0.001
White matter volume	-0.08 (-0.12;-0.03)	0.002
Subcortical structures		
Left amygdala	-0.03 (-0.08;0.02)	0.205
Right amygdala	-0.06 (-0.11;-0.01)	0.028
Left hippocampus	-0.04 (-0.09;0.02)	0.183
Right hippocampus	-0.02 (-0.07;0.03)	0.438
Left thalamus	0.00 (-0.07;0.06)	0.885
Right thalamus	-0.03 (-0.10;0.03)	0.281
Left caudate	-0.03 (-0.08;0.02)	0.194
Right caudate	-0.04 (-0.09;0.01)	0.104
Left putamen	-0.02 (-0.07;0.03)	0.452
Right putamen	-0.04 (-0.05;0.05)	0.860
Left globus pallidus	-0.01 (-0.06;0.04)	0.674
Right globus pallidus	-0.02 (-0.07;0.02)	0.332
Left nucleus accumbens	0.03 (-0.02;0.07)	0.295
Right nucleus accumbens	0.01 (-0.04;0.06)	0.628
White matter microstructural measures (*N* = 2059)		
Global fractional anisotropy (FA)	0.01 (-0.03;0.05)	0.663
Global mean diffusivity (MD)	-0.07 (-0.11;-0.02)	0.007

Note: All analyses are corrected for child sex, child age at MRI visit, child ethnicity, maternal educational level, and maternal psychopathology scores. Subcortical volumes are additionally adjusted for intracranial volume. Estimates reflect standardized coefficients.

Supplementary Table S5: Vertex-wise analyses of gyrification and callous traits (*N* = 2146)

Hemisphere and region	Cluster size (mm^2)	Talairach Coordinates (x, y, z)	Number of Vertices within Cluster	Cluster-wise *P*-values
Left				
Superior temporal	608.64	-51.8, -6.8, -4.9	1312	0.0018
Middle temporal	540.78	-54.9, -27.2, -12.5	1068	0.0034
Right				
Middle temporal	1377.31	46.2, -59.9, 6.7	2978	0.0001

Note: Analyses are corrected for age, sex, child ethnicity and maternal educational level.

Supplementary Table S6: Vertex-wise analyses of cortical surface area and callous traits, with additional adjustment co-occurring emotional and behavioral problems (*N* = 2146).

Hemisphere and region	Cluster size (mm^2)	Talairach Coordinates (x, y, z)	Number of Vertices within Cluster	β (average across cluster)	Cluster-wise *P*-values
Left					
1. Superior frontal	604.95	-13.5, 46.5, 4.4	1096	-0.07	0.0006

Note: Analyses are corrected for age, sex, child ethnicity and maternal educational level. Numbers of the clusters correspond to the numbers shown in Figure 1. Cluster forming threshold of 0.001.

Supplementary Table S7: Vertex-wise analyses of cortical surface area and callous traits, with additional adjustment for non-verbal IQ (*N* = 2146).

Hemisphere and region	Cluster size (mm^2)	Talairach Coordinates (x, y, z)	Number of Vertices within Cluster	β (average across cluster)	Cluster-wise *P*-values
Left					
1. Fusiform	1334.24	-41.8, -47.3, -14.0	2218	-0.08	0.0001
2. Superior temporal	684.41	-51.6, 8.7, -18.0	1278	-0.06	0.0003
3. Lingual	543.88	-20.3, -53.9, -3.1	1150	-0.06	0.0012
4. Superior frontal	445.83	-13.4, 46.0, 4.0	836	-0.05	0.0040
Right					
5. Middle temporal	1197.06	49.7, 7.2, -32.3	2061	-0.06	0.0001
6. Isthmus of cingulate	326.15	6.0, -50.1, 20.9	818	-0.07	0.0188
7. Post-central	310.58	60.0, -8.2, 15.9	671	-0.06	0.0218

Note: Analyses are corrected for age, sex, child ethnicity and maternal educational level. Numbers of the clusters correspond to the numbers shown in Figure 1. Cluster forming threshold of 0.001.

Supplementary Table S8: Vertex-wise analyses of cortical surface area and callous traits, with additional adjustment maternal psychiatric problems (*N* = 2146).

Hemisphere and region	Cluster size (mm^2)	Talairach Coordinates (x, y, z)	Number of Vertices within Cluster	β (average across cluster)	Cluster-wise *P*-values
Left					
1. Inferior temporal	1176.29	-45.6, -62.3, -6.0	1976	-0.05	0.0001
2. Superior frontal	524.18	-13.7, 45.9, 3.5	995	-0.04	0.0011
3. Lingual	482.47	-20.3, -53.9, -3.1	1025	-0.07	0.0032
4. Superior temporal	477.69	-51.8, 8.0, -18.0	907	-0.06	0.0032
5. Lateral orbitofrontal	369.63	-31.7, 26.3, -10.6	753	-0.05	0.0109
Right					
6. Middle temporal	1163.62	50.2, 7.3, -32.8	2017	-0.06	0.0001

Note: Analyses are corrected for age, sex, child ethnicity and maternal educational level. Numbers of the clusters correspond to the numbers shown in Figure 1. Cluster forming threshold of 0.001.

Supplementary Table S9: Association of global white matter axial diffusivity (AD) and radial diffusivity (RD) with callous traits.

	Callous traits	
	β (95% CI)	*P*
White matter microstructural measures (*N* = 2059)		
Global axial diffusivity (AD)	-0.06 (-0.12;-0.02)	0.003
Global radial diffusivity (RD)	-0.05 (-0.09;0.00)	0.043

Note: All analyses are corrected for child sex, child age at MRI visit, child ethnicity, maternal educational level, and CBCL total problems scores. Estimates reflect standardized coefficients.

Supplementary Table S10: Associations between mean diffusivity (MD) in individual white matter tracts and callous traits, with additional adjustment for co-occurring emotional and behavioral problems.

	Interpersonal callousness traits	
	β (95% CI)	*P*
Inferior longitudinal fasciculus	-0.03 (-0.07;0.01)	0.150
Superior longitudinal fasciculus	-0.06 (-0.10;-0.02)	0.005
Forceps minor	-0.05 (-0.09;-0.01)	0.026
Forceps major	-0.02 (-0.06;0.02)	0.393
Corticospinal tract	-0.14 (-0.24;-0.04)	0.008
Uncinate fasciculus	-0.06 (-0.10;-0.02)	0.004
Cingulum bundle	-0.05 (-0.09;-0.01)	0.011

Note: All analyses are corrected for child sex, child age at MRI visit, child ethnicity, maternal educational level, and CBCL total problems scores. Microstructural properties of left and right tracts were combined and weighted for their respective volumes, except for forceps minor and major. Estimates reflect standardized coefficients.

Supplementary Table S11: Associations between mean diffusivity (MD) in individual white matter tracts and callous traits, with additional adjustment for non-verbal IQ.

	Interpersonal callousness traits	
	β (95% CI)	*P*
Inferior longitudinal fasciculus	-0.04 (-0.09;0.00)	0.066
Superior longitudinal fasciculus	-0.06 (-0.11;-0.02)	0.007
Forceps minor	-0.04 (-0.08;0.00)	0.072
Forceps major	-0.02 (-0.06;0.03)	0.500
Corticospinal tract	-0.15 (-0.27;-0.04)	0.008
Uncinate fasciculus	-0.07 (-0.11;-0.03)	0.002
Cingulum bundle	-0.06 (-0.10;-0.01)	0.013

Note: All analyses are corrected for child sex, child age at MRI visit, child ethnicity, maternal educational level, and non-verbal IQ of the child. Microstructural properties of left and right tracts were combined and weighted for their respective volumes, except for forceps minor and major. Estimates reflect standardized coefficients.

Supplementary Table S12: Associations between mean diffusivity (MD) in individual white matter tracts and callous traits, with additional adjustment for maternal psychiatric problems.

	Interpersonal callousness traits	
	β (95% CI)	*P*
Inferior longitudinal fasciculus	-0.04 (-0.09;0.01)	0.102
Superior longitudinal fasciculus	-0.06 (-0.10;-0.01)	0.012
Forceps minor	-0.04 (-0.08;0.00)	0.066
Forceps major	-0.02 (-0.06;0.03)	0.392
Corticospinal tract	-0.15 (-0.26;-0.04)	0.007
Uncinate fasciculus	-0.07 (-0.11;-0.02)	0.003
Cingulum bundle	-0.05 (-0.10;-0.01)	0.014

Note: All analyses are corrected for child sex, child age at MRI visit, child ethnicity, maternal educational level, and non-verbal IQ of the child. Microstructural properties of left and right tracts were combined and weighted for their respective volumes, except for forceps minor and major. Estimates reflect standardized coefficients.

Supplementary Table S13: Associations between axial diffusivity (AD) and radial diffusivity (RD) in individual white matter tracts and callous traits.

	β (95% CI)	P	FDR-adjusted P
Inferior longitudinal fasciculus			
Axial diffusivity (AD)	-0.07 (-0.12;-0.03)	0.002	0.007
Radial diffusivity (RD)	-0.01 (-0.05;0.04)	0.693	0.795
Superior longitudinal fasciculus			
Axial diffusivity (AD)	-0.07 (-0.12;-0.03)	0.002	0.007
Radial diffusivity (RD)	-0.04 (-0.09;0.00)	0.066	0.116
Forceps minor			
Axial diffusivity (AD)	-0.01 (-0.05;0.03)	0.655	0.764
Radial diffusivity (RD)	-0.04 (-0.08;0.00)	0.031	0.072
Forceps major			
Axial diffusivity (AD)	-0.01 (-0.06;0.03)	0.609	0.764
Radial diffusivity (RD)	-0.01 (-0.06;0.04)	0.795	0.795
Corticospinal tract			
Axial diffusivity (AD)	-0.23 (-0.41;-0.05)	0.011	0.026
Radial diffusivity (RD)	-0.02 (-0.07;0.02)	0.310	0.434
Uncinate fasciculus			
Axial diffusivity (AD)	-0.04 (-0.08;0.01)	0.116	0.203
Radial diffusivity (RD)	-0.06 (-0.10;-0.02)	0.007	0.025
Cingulum bundle			
Axial diffusivity (AD)	0.00 (-0.04;0.04)	0.987	0.987
Radial diffusivity (RD)	-0.06 (-0.11;-0.02)	0.004	0.025

Note: All analyses are corrected for child sex, child age at MRI visit, child ethnicity, and maternal educational level. Microstructural properties of left and right tracts were combined and weighted for their respective volumes, except for forceps minor and major. Estimates reflect standardized coefficients.

Supplementary Table S14: Endorsement of the mother-reported callous traits items in boys only (*n* = 1071).

	Does not apply at all, *n* (%)	Does apply slightly, *n* (%)	Does apply very much, *n* (%)	Does apply completely, *n* (%)
Cannot be trusted with regard to what he/she says*	825 (77.1)	222 (20.7)	15 (1.4)	8 (0.7)
Denies having done something wrong, even though it is certain he/she did do something wrong*	521 (48.6)	505 (47.1)	37 (3.4)	10 (0.9)
Uses or misleads other people in order to get what he/she wants	894 (83.2)	168 (15.6)	7 (0.7)	6 (0.6)
If confronted about his/her behaviour, he/she is able to talk him/herself out of it easily*	549 (51.4)	407 (38.1)	93 (8.7)	20 (1.9)
Does not keep any promises*	672 (63.0)	362 (34.0)	24 (2.3)	8 (0.8)
Does not find other people's feelings important*	865 (80.8)	174 (16.2)	24 (2.2)	8 (0.7)
Is cold and indifferent	1001 (93.6)	61 (5.7)	6 (0.6)	2 (0.2)

* Significantly higher endorsement frequencies in boys compared with girls as assessed with chi-square difference tests ($P < 0.05$)

Supplementary Table S15: Endorsement of the mother-reported callous traits items in girls only (*n* = 1075).

	Does not apply at all, *n* (%)	Does apply slightly, *n* (%)	Does apply very much, *n* (%)	Does apply completely, *n* (%)
Cannot be trusted with regard to what he/she says*	896 (84.0)	160 (15.0)	6 (0.6)	5 (0.5)
Denies having done something wrong, even though it is certain he/she did do something wrong*	625 (58.5)	417 (39.0)	21 (2.0)	5 (0.5)
Uses or misleads other people in order to get what he/she wants	890 (83.4)	162 (15.2)	13 (1.2)	2 (0.2)
If confronted about his/her behaviour, he/she is able to talk him/herself out of it easily*	625 (58.9)	338 (31.9)	73 (6.9)	25 (2.4)
Does not keep any promises*	756 (70.8)	285 (26.7)	22 (2.1)	5 (0.5)
Does not find other people's feelings important*	936 (87.6)	112 (10.5)	16 (1.5)	5 (0.5)
Is cold and indifferent	1016 (95.3)	44 (4.1)	3 (0.3)	3 (0.3)

* Significantly lower endorsement frequencies in girls compared with boys as assessed with chi-square difference tests ($P < 0.05$)

Supplementary Table S16: Correlations between callous traits and behavioral traits, stratified by sex

	Boys	Girls
Non-verbal IQ at age 6 years, mean (SD)	-0.11**	-0.04
Mother-reported CBCL, median (IQR)		
Affective Problems	0.23**	0.22**
Anxiety Problems	0.16**	0.14**
Somatic Complaints	0.11**	0.07**
ADHD Problems	0.38**	0.31**
ODD Problems	0.41**	0.36**
CD Problems	0.51**	0.39**
Child-reported BPM, median (IQR)		
Internalizing problems	0.09**	0.08**
Externalizing problems	0.24**	0.19**
Attention problems	0.19**	0.20**
SDQ – Prosocial scale, median (IQR)		
Mother-reported	-0.24**	-0.18**
Child-reported	-0.09**	-0.12**

** $P < 0.001$

Supplementary Table S17: Association of interaction of child sex with global structural volumetric and global white matter microstructural measures on callous traits.

	Callous traits	
	β (95% CI)	*P*
Structural volumetric measures (*N* = 2146)		
Total brain volume	0.02 (-0.08;0.12)	0.700
Cortical grey matter volume	0.03 (-0.08;0.12)	0.577
White matter volume	0.00 (-0.10;0.09)	0.951
Subcortical structures		
Right amygdala	-0.04 (-0.13;0.05)	0.382
White matter microstructural measures (*N* = 2059)		
Global mean diffusivity (MD)	-0.13 (-0.22;-0.04)	0.005

Note: Sex interaction was only explored for those indices for which a main association was observed. All analyses are corrected for child sex, child age at MRI visit, child ethnicity, maternal educational level. Amygdala volume is additionally adjusted for intracranial volume. Estimates reflect standardized coefficients for the interaction term.

Supplementary Table S18: Associations between global white matter microstructural measures and callous traits, stratified by sex.

	Callous traits	
	β (95% CI)	*P*
Boys (*n* = 1028)		
Global mean diffusivity (MD)	0.00 (-0.07;0.06)	0.878
Girls (*n* = 1031)		
Global mean diffusivity (MD)	-0.13 (-0.20;-0.07)	<0.001
Global axial diffusivity (AD)	-0.10 (-0.16;-0.03)	0.003
Global radial diffusivity (RD)	-0.12 (-0.18;-0.05)	<0.001

Note: All analyses are corrected for child sex, child age at MRI visit, child ethnicity, maternal educational level. Estimates reflect standardized coefficients.

Supplementary Table S19: Associations of individual white matter mean diffusivity, axial diffusivity and radial diffusivity with callous traits, shown for girls only (*n* = 1031).

	Callous traits	
	β (95% CI)	*P*
Inferior longitudinal fasciculus		
Mean diffusivity	-0.09 (-0.16;-0.02)	0.009
Axial diffusivity	-0.08 (-0.14;-0.01)	0.017
Radial diffusivity	-0.07 (-0.014;-0.01)	0.033
Superior longitudinal fasciculus		
Mean diffusivity	-0.15 (-0.21;-0.08)	<0.001
Axial diffusivity	-0.12 (-0.19;-0.06)	<0.001
Radial diffusivity	-0.12 (-0.18;-0.05)	<0.001
Forceps minor		
Mean diffusivity	-0.08 (-0.14;-0.02)	0.011
Axial diffusivity	0.00 (-0.05;0.06)	0.921
Radial diffusivity	-0.09 (-0.15;-0.03)	0.002
Forceps major		
Mean diffusivity	-0.04 (-0.11;0.02)	0.174
Axial diffusivity	-0.04 (-0.11;0.02)	0.170
Radial diffusivity	-0.03 (-0.10;0.03)	0.281
Corticospinal tract		
Mean diffusivity	-0.30 (-0.46;-0.14)	<0.001
Axial diffusivity	-0.30 (-0.56;-0.05)	0.020
Radial diffusivity	-0.07 (-0.13;-0.01)	0.029
Uncinate fasciculus		
Mean diffusivity	-0.10 (-0.16;-0.04)	0.002
Axial diffusivity	-0.06 (-0.12;0.01)	0.080
Radial diffusivity	-0.08 (-0.14;-0.02)	0.011
Cingulum bundle		
Mean diffusivity	-0.11 (-0.17;-0.05)	<0.001
Axial diffusivity	-0.02 (-0.08;0.04)	0.547
Radial diffusivity	-0.11 (-0.17;-0.05)	<0.001

Note: All analyses are corrected for child age at MRI visit, child ethnicity, and maternal educational level. Microstructural properties of left and right tracts were combined and weighted for their respective volumes, except for forceps minor and major. Estimates reflect standardized coefficients.

Supplementary Table S20: Associations of child conduct problems by callous traits interaction on global structural volumetric and global white matter microstructural measures.

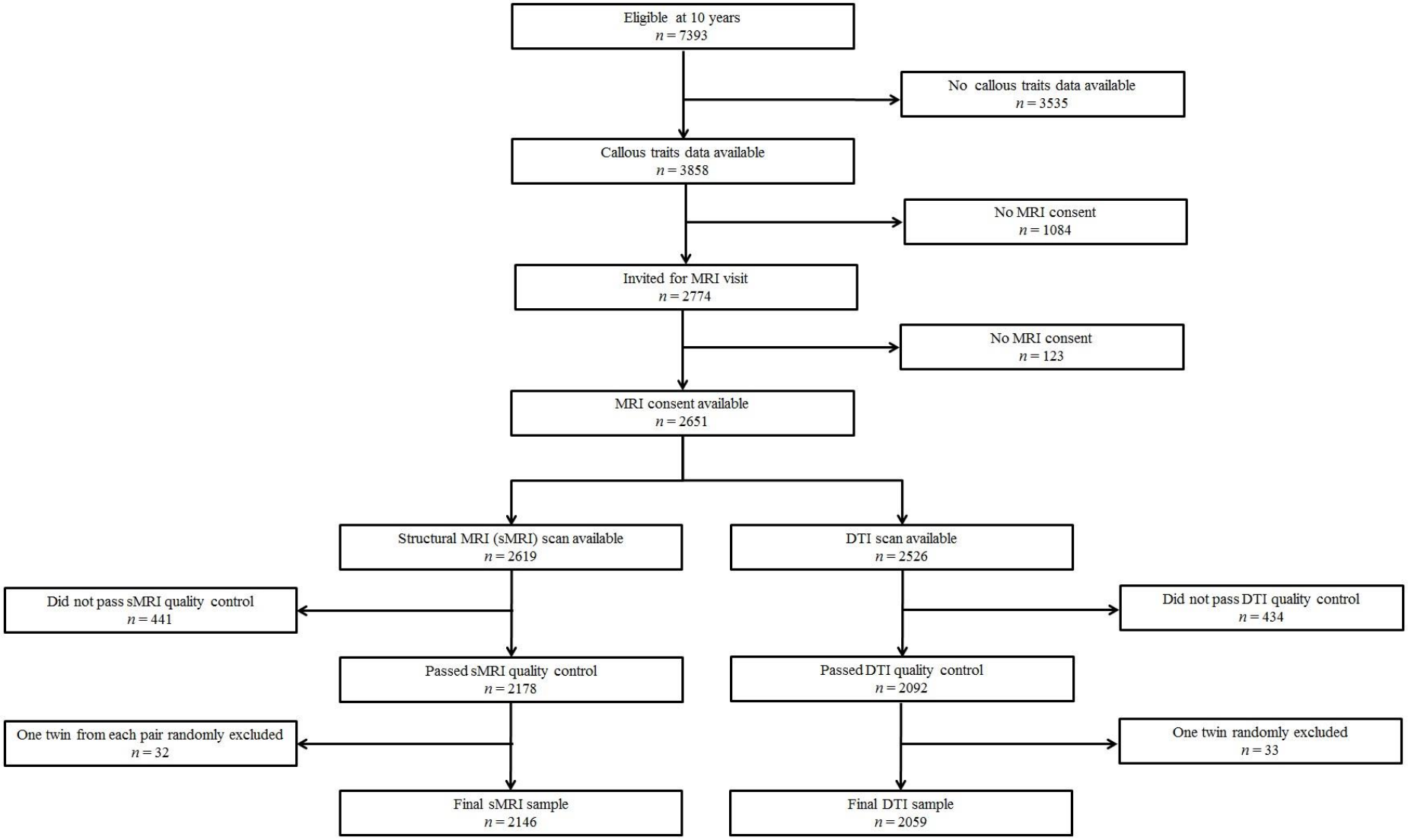
	Callous traits	
	β (95% CI)	*P*
Structural volumetric measures (*N* = 2146)		
Total brain volume	-0.01 (-0.04;0.03)	0.726
Cortical grey matter volume	0.00 (-0.04;0.04)	0.976
White matter volume	0.00 (-0.04;0.03)	0.806
Subcortical structures		
Right amygdala	0.03 (-0.01;0.07)	0.111
White matter microstructural measures (*N* = 2059)		
Global mean diffusivity (MD)	0.02 (-0.02;0.07)	0.204

Note: Sex interaction was only explored for those indices for which a main association was observed. All analyses are corrected for child sex, child age at MRI visit, child ethnicity, and maternal educational level. Amygdala volume is additionally adjusted for intracranial volume. Estimates reflect standardized coefficients for the interaction term.

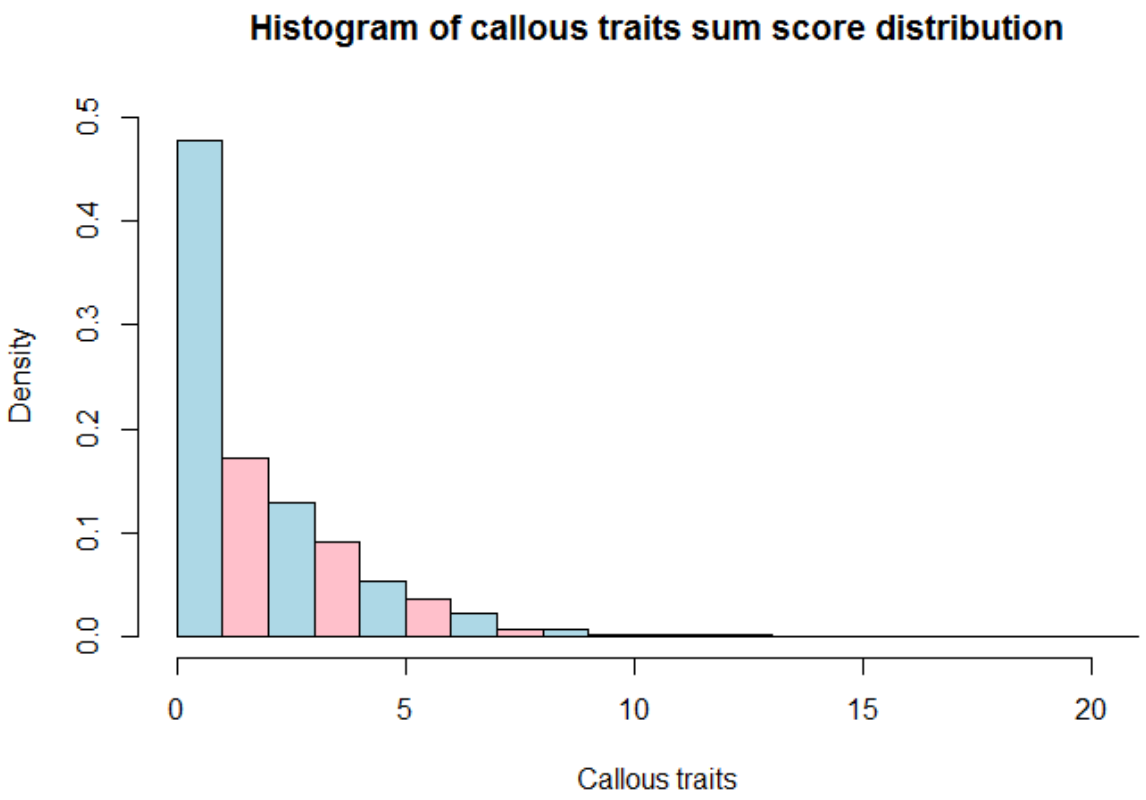
Supplementary Table S21: Association of global structural volumetric and global white matter microstructural measures with callous traits, testing for non-linear (quadratic) associations.

	Callous traits	
	β (95% CI)	*P*
Structural volumetric measures (*N* = 2146)		
Total brain volume	-0.02 (-0.05;0.01)	0.189
Cortical grey matter volume	-0.02 (-0.05;0.01)	0.187
White matter volume	-0.02 (-0.05;0.01)	0.285
Subcortical structures		
Left amygdala	-0.01 (-0.04;0.02)	0.358
Right amygdala	0.00 (-0.03;0.02)	0.741
Left hippocampus	-0.02 (-0.05;0.04)	0.093
Right hippocampus	-0.01 (-0.04;0.01)	0.251
Left thalamus	-0.01 (-0.04;0.02)	0.503
Right thalamus	0.00 (-0.03;0.03)	0.921
Left caudate	0.00 (-0.03;0.02)	0.763
Right caudate	-0.02 (-0.04;0.01)	0.269
Left putamen	0.00 (-0.03;0.03)	0.941
Right putamen	-0.01 (-0.04;0.01)	0.329
Left globus pallidus	-0.02 (-0.04;0.01)	0.240
Right globus pallidus	-0.01 (-0.04;0.01)	0.395
Left nucleus accumbens	0.00 (-0.02;0.03)	0.840
Right nucleus accumbens	-0.01 (-0.04;0.02)	0.458
White matter microstructural measures (*N* = 2059)		
Global fractional anisotropy (FA)	0.02 (-0.02;0.05)	0.320
Global mean diffusivity (MD)	0.02 (-0.01;0.05)	0.183

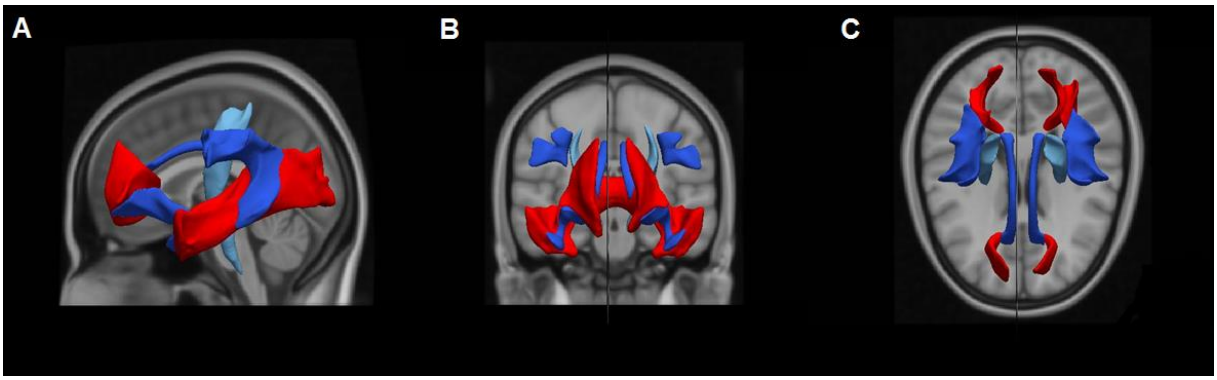
Note: All analyses are corrected for child sex, child age at MRI visit, child ethnicity, maternal educational level, and non-verbal IQ of the child. Sub-cortical volumes are additionally adjusted for intracranial volume. Estimates reflect standardized coefficients.



Supplementary Figure S1: Inclusion flow chart of the current study sample



Supplementary Figure S2: Histogram of the endorsement distribution of callous traits (*N* = 2146)



Supplementary Figure S3: Associations between individual white matter tracts mean diffusivity (MD) and callous traits (N = 2059).

Note: Panel A shows the sagittal view, panel B the coronal view, and panel C the transversal view. Non-significant associations are depicted in red, positive associations are depicted in yellow, and negative associations are depicted in blue. The brighter the color, the stronger the association.

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